Pioglitazone Prevents Diabetes in Patients With Insulin Resistance and Cerebrovascular Disease

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OBJECTIVE

The Insulin Resistance Intervention after Stroke (IRIS) trial recently found that pioglitazone reduced risk for stroke and myocardial infarction in patients with insulin resistance but without diabetes who had had a recent ischemic stroke or transient ischemic attack (TIA). This report provides detailed results on the metabolic effects of pioglitazone and the trial's prespecified secondary aim of diabetes prevention.

RESEARCH DESIGN AND METHODS

A total of 3,876 patients with recent ischemic stroke or TIA, no history of diabetes, fasting plasma glucose (FPG) <126 mg/dL, and insulin resistance by homeostasis model assessment of insulin resistance (HOMA-IR) score >3.0 were randomly assigned to pioglitazone or placebo. Surveillance for diabetes onset during the trial was accomplished by periodic interviews and annual FPG testing.

RESULTS

At baseline, the mean FPG, HbA_{1c}, insulin, and HOMA-IR were 98.2 mg/dL (5.46 mmol/L), 5.8% (40 mmol/mol), 22.4 μIU/mL, and 5.4, respectively. After 1 year, mean HOMA-IR and FPG decreased to 4.1 and 95.1 mg/dL (5.28 mmol/L) in the pioglitazone group and rose to 5.7 and 99.7 mg/dL (5.54 mmol/L), in the placebo group (all $P < 0.0001$). Over a median follow-up of 4.8 years, diabetes developed in 73 (3.8%) participants assigned to pioglitazone compared with 149 (7.7%) assigned to placebo (hazard ratio [HR] 0.48 [95% CI 0.33–0.69]; $P < 0.0001$). This effect was predominately driven by those with initial impaired fasting glucose (FPG >100 mg/dL [5.6 mmol/L]; HR 0.41 [95% CI 0.30–0.57]) or elevated HbA_{1c} (>5.7% [39 mmol/mol]; HR 0.46 [0.34–0.62]).

CONCLUSIONS

Among patients with insulin resistance but without diabetes who had had a recent ischemic stroke or TIA, pioglitazone decreased the risk of diabetes while also reducing the risk of subsequent ischemic events. Pioglitazone is the first medication shown to prevent both progression to diabetes and major cardiovascular events as prespecified outcomes in a single trial.

Globally, >410 million patients are now estimated to have type 2 diabetes, and the prevalence of this condition continues to increase. By 2040, it is expected that this figure will rise to 642 million (1). Complications, including atherosclerosis, nephropathy, neuropathy, and retinopathy, make diabetes a major cause of morbidity, mortality, and costs. Although treatments for type 2 diabetes continue to improve, clinicians and public health experts agree that the most effective way to reduce its

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**A complete list of the IRIS Trial Investigators can be found in the Supplementary Data online.*

sequelae is through its prevention (2,3). Type 2 diabetes is preceded by a prolonged phase of insulin resistance and mildly elevated blood glucose levels, sometimes referred to as prediabetes. This opens the possibility for preventive strategies, with most focusing on improving insulin resistance as a core pathophysiological defect (4). Weight loss and several drugs, including metformin and thiazolidinediones (2,5), have been effective in preventing (or delaying) the onset of diabetes. However, no therapy other than lifestyle changes has gained wide acceptance in part because of a lack of confirmed benefit on clinical cardiovascular outcomes, despite the fact that prediabetes is a recognized risk factor for cardiovascular disease (5).

The purpose of this report is to examine the effect of the thiazolidinedione pioglitazone on prevention of diabetes in patients with recent cerebrovascular event who were enrolled in the Insulin Resistance Intervention after Stroke (IRIS) trial. The primary aim of IRIS was to test the hypothesis that pioglitazone reduces the risk of cardiovascular events in patients without diabetes who had insulin resistance along with a recent ischemic stroke or transient ischemic attack (TIA) (6). Prevention of diabetes was a planned secondary outcome. As previously reported, IRIS found that pioglitazone, compared with placebo, reduced the hazard of stroke or myocardial infarction by 24% (hazard ratio [HR] 0.76 [95% CI 0.62–0.93]; $P = 0.007$) (7). Pioglitazone also reduced the hazard of diabetes by 52% (HR 0.48 [95% CI 0.33–0.69]; $P < 0.0001$ (7). More than half of IRIS participants had fasting plasma glucose (FPG) $<$100 mg/dL (5.6 mmol/L) at baseline, and 35% had an HbA_{1c} level $<$5.7% (39 mmol/mol), both cut points used to define the presence or absence of prediabetes. In this analysis, we report in greater detail on metabolic outcomes in IRIS and the efficacy of pioglitazone in preventing diabetes according to baseline glycemic measures.

RESEARCH DESIGN AND METHODS

Overall Study Design

A summary of the trial methods, full protocol, and statistical plan have been previously published (6). Briefly, the IRIS trial was funded by the U.S. National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health. Pioglitazone and matching placebo were provided by Takeda Pharmaceuticals International, Inc., which had no role in protocol development, trial conduct, data interpretation, or manuscript drafting. Clinical research activities, central pharmacy operations, data collection, regulatory compliance, and site monitoring were coordinated by the Yale School of Medicine. Enrollment and follow-up of participants occurred at 179 sites in Australia, Canada, Germany, Israel, Italy, the U.K., and the U.S. Trial operations at research sites were approved by local institutional review boards. The trial was conducted according to a protocol that was approved by an independent Data and Safety Monitoring Board appointed by the NINDS.

Study Participants

Eligible patients were at least 40 years of age with a qualifying ischemic stroke or TIA within 6 months prior to randomization. Additional major eligibility criteria were the biochemical demonstration of insulin resistance on a screening blood test. We defined insulin resistance with the HOMA of insulin resistance (HOMA-IR) score (calculated as [fasting insulin, μU/mL × fasting glucose, mmol/L]/22.5) (8). A HOMA-IR threshold of $>$3.0 was chosen to define the qualifying level of insulin resistance because this value represented the highest quartile of values among populations without diabetes (7). Because insulin sensitivity could conceivably be impaired transiently after stroke due to tissue inflammation or acute decrease in physical activity, the screening was performed ≥14 days after the index event. Patients were excluded if they had previously diagnosed diabetes and were using pharmacological antihyperglycemic therapy or if, at the screening visit, the HbA_{1c} was ≥7.0% (53 mmol/mol) or the FPG was ≥126 mg/dL (7.0 mmol/L), repeated and confirmed. These trial criteria were developed in 2004. In 2010, the American Diabetes Association (ADA) updated its diagnostic criteria for diabetes to include an HbA_{1c} ≥6.5% (9). It was initially recognized that the protocol might allow patients with early or mild diabetes to enroll. Potential randomization to placebo was felt to be justified, however, because their baseline HbA_{1c} was below the level of 7.0% (53 mmol/mol), which many would consider a reasonable threshold for the initiation of glucose-lowering therapy.

As previously detailed (6), excluded conditions included heart failure, bladder cancer or high risk for bladder cancer, moderate to severe dependent pitting edema, irreversible medical condition with predicted survival $<$4 years, and oral corticosteroid use.

Study Procedures

Eligible participants were randomly assigned in a 1:1 ratio to receive pioglitazone or placebo. During the first 3 months, researchers contacted participants every 2 weeks to assess adherence to study drug and potential adverse or outcome events. The initial study drug dose was 15 mg daily or matching placebo. For participants who reported no new or worsening edema, shortness of breath, or excessive weight gain, study medication was increased to 30 mg daily at week 4 and then to 45 mg at week 8.

Beginning at month four, researchers contacted participants quarterly. Participation ended at 5 years or the last contact before trial end in July 2015. Annual in-person visits included detailed medication review and physical examinations. At the baseline and first annual visit, blood was drawn fasting for insulin, glucose, lipids, and alanine aminotransferase. FPG was measured at subsequent annual visits. Patients with values ≥126 mg/dL (7.0 mmol/L) were asked to return to the study site for a repeat test for confirmation. HbA_{1c} was not measured beyond the screening visit (used to exclude those with levels ≥7.0% [53 mmol/mol]). Oral glucose tolerance testing (OGTT) was not performed.

If participants reported new or excessive weight gain or edema or shortness of breath, researchers managed them according to algorithms developed by the IRIS Operations Committee. These included instructions for study drug dose reduction if weight gain or edema persisted despite usual interventions or to assist in the ongoing participation of the patient in the trial. However, study drug was permanently discontinued for heart failure (10), bladder cancer (11), or a second low-energy bone fracture. If diabetes was diagnosed during follow-up, patients could remain on study drug unless open-label thiazolidinedione was prescribed by their personal physicians.

Diabetes Outcome Definition

The diagnosis of diabetes was a prespecified secondary outcome, adjudicated by an independent committee of diabetes experts blinded to treatment assignment. The outcome of diabetes was defined according to the ADA guidelines prevailing at trial initiation (12):

1. Two FPG measurements ≥126 mg/dL (7.0 mmol/L) or
2. Two random plasma glucose ≥200 mg/dL (11.1 mmol/L) in the presence of typical symptoms of hyperglycemia.

In addition, diabetes could also be diagnosed in the presence of compelling indicators of hyperglycemia, including:

1. A personal physician diagnoses of diabetes, accompanied by the prescription of an antihyperglycemic drug with any of the following single test results:
   a. FPG ≥126 mg/dL (7.0 mmol/L)
   b. Random plasma glucose ≥200 mg/dL (11.1 mmol/L);
   c. 2-h OGTT plasma glucose ≥200 mg/dL (11.1 mmol/L);
   d. HbA_{1c} ≥7.0%.
2. A diagnosis of diabetes made during a hospital admission if the hospitalization was for diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome or if the patient was discharged on an antihyperglycemic agent and the HbA_{1c} was ≥7.0% during the hospitalization.
3. Two fasting capillary blood glucose values obtained with a point-of-care meter in a health-care setting ≥151 mg/dL (8.4 mmol/L) (i.e., conservatively chosen to allow for a 20% margin above the usual threshold of 126 mg/dL [7 mmol/L], based on the acceptable accuracy margin of available point-of-care meters) (13).
4. Two random capillary blood glucose values obtained with a point-of-care meter in a health-care setting ≥240 mg/dL (13.2 mmol/L) (i.e., conservatively chosen to allow for a 20% margin above the usual threshold of 200 mg/dL [11.1 mmol/L]), in the presence of typical symptoms of hyperglycemia.

In 2010, the ADA updated its diagnostic criteria for diabetes to include HbA_{1c} ≥6.5% (9). To determine how the IRIS trial results would be affected by use of this revised definition, an ancillary sensitivity analysis was conducted that included HbA_{1c} ≥6.5% values if obtained and documented by the patient's personal physician.

Statistical Analysis

The analysis of time to onset of diabetes was performed according to the intention-to-treat principle. The effect of pioglitazone relative to placebo was estimated as an HR (with 95% confidence limits) from the Cox model (14). Cumulative event-free rates were calculated by the method of Kaplan-Meier (15) and tested by the log-rank statistic using a type I error of 0.05. The Hochberg procedure was used to adjust significance levels and CIs using an overall type I error of 0.05 (two-sided) (16). The effect of pioglitazone on development of diabetes was further assessed within selected baseline subgroups and according to the degree of adherence to the study drug. These subgroup analyses were not prespecified in the IRIS protocol and have not been adjusted for multiple comparisons. SAS version 9.3 was used for all analyses (SAS Institute Inc., Cary, NC).

RESULTS

Study Population

A total of 3,895 patients were randomized at 179 sites in seven countries between February 2005 and January 2013. After the removal of patients at one site with consent process irregularities, 3,876 patients comprised the final analysis cohort. During a median follow-up of 4.8 years, 117 of 1,939 participants assigned to pioglitazone and 110 of 1,937 participants assigned to placebo withdrew consent. During the same interval, 58 and 41 were lost to follow-up in each group, respectively. Total participant-years of follow-up were 7,951 in the pioglitazone group and 7,952 in the placebo group.

Baseline Characteristics

Baseline characteristics of the IRIS cohort were comparable in both treatment groups (Table 1 and Supplementary Table 1). The mean age was 63.5 ± 10.6 years, 65% were male, and mean BMI 30.0 ± 5.4 kg/m^2. The mean baseline FPG was 98.2 ± 10.0 mg/dL (5.46 ± 0.56 mmol/L), HbA_{1c} 5.8 ± 0.4%, fasting insulin level 22.4 ± 10.3 μIU/mL, and HOMA-IR 5.4 ± 2.7. Based on the prevailing prediabetes diagnostic criteria of the ADA (12), 41.6% had impaired fasting glucose (IFG) (FPG 100–125 mg/dL [5.6–6.9 mmol/L]); based on the more restrictive criteria of the World Health Organization (WHO) and International Diabetes Federation (IDF), 13.5% had IFG (FPG 110–125 mg/dL [6.1–6.9 mmol/L]). In addition, 64.9% of the cohort had an HbA_{1c} ≥5.7%, a cut point recognized by the ADA as conferring increased risk for diabetes and also categorized as prediabetes. Of note, 6.3% of the IRIS cohort had an HbA_{1c} ≥6.5% (but <7.0%), which, if confirmed on a repeat test, would have met the 2010 ADA diabetes criteria (9).

The study cohort had additional features of the metabolic syndrome, with a mean waist circumference of 104.9 ± 12.8 cm in men and 99.2 ± 14.3 cm in women, triglyceride levels of 141 ± 73 mg/dL (1.59 ± 0.82 mmol/L), and HDL cholesterol levels of 44 ± 11 mg/dL (1.14 ± 0.28 mmol/L) in men and 53 ± 13 mg/dL (1.37 ± 0.34 mmol/L) in women. At baseline, 80% of participants had a blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or reported a history of hypertension being managed pharmacologically. In all, ~52% of participants met criteria for the metabolic syndrome, based on the 2005 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria (17) (Table 1).

Clinical features of the study participants categorized by baseline glycemic/metabolic status are shown in Supplementary Table 2. In general, patients with IFG (ADA, ≥100 mg/dL [5.6 mmol/L]), increased HbA_{1c} (≥5.7%), and HOMA-IR above the median (>4.6) had a higher prevalence of metabolic syndrome features than those without these states.

Diabetes and Metabolic Outcomes

In patients with values both at baseline and at 1 year, mean HOMA-IR declined by 24% from 5.4 ± 2.6 to 4.1 ± 2.8 in the pioglitazone group and increased by 7% from 5.3 ± 2.6 to 5.7 ± 6.6 in the placebo group ($P < 0.0001$), consistent with the study drug's recognized insulin-sensitizing effects. Mean FPG decreased from 98.2 ± 10.0 mg/dL (5.46 ± 0.56 mmol/L) to 95.1 ± 11.0 mg/dL (5.28 ± 0.61 mmol/L) with pioglitazone, whereas it increased from 98.3 ± 9.9 mg/dL (5.46 ± 0.55 mmol/L) to

Table 1—Baseline metabolic characteristics by treatment group

Characteristic	Pioglitazone (*N* = 1,939)	Placebo (*N* =1,937)
Laboratory data, mean (SD)		
Fasting glucose (mg/dL)	98.3 (10.0)	98.2 (9.9)
Insulin (μU/mL)	22.5 (10.4)	22.2 (10.1)
HOMA-IR	5.5 (2.8)	5.4 (2.7)
HbA_{1c} (%)	5.8 (0.4)	5.8 (0.4)
Dysglycemic categories, *n* (%)		
ADA IFG (≥100 mg/dL [5.6 mmol/L])	813 (41.9)	800 (41.3)
WHO/IDF IFG (≥110 mg/dL [6.1 mmol/L])	267 (13.8)	257 (13.3)
HbA_{1c} ≥5.7% (39 mmol/mol)	1,266 (65.3)	1,247 (64.4)
HbA_{1c} 6.5 to <7.0% (48–53 mmol/mol)	116 (6.0)	129 (6.7)
NCEP ATP-III metabolic syndrome features, *n* (%)		
ADA IFG (≥100 mg/dL [5.6 mmol/L])	813 (41.9)	800 (41.3)
Antihypertensive medication or SBP/DBP ≥130/≥85 mmHg	1,558 (80.5)	1,555 (80.4)
Abdominal obesity*	1,173 (61.2)	1,212 (63.1)
HDL <40/50 mg/dL (1.03/1.29 mmol/L) for men/women	787 (40.7)	785 (40.6)
Triglycerides ≥150 mg/dL (1.69 mmol/L)	675 (34.9)	641 (33.1)
Number(s) of features present		
1 or more	1,845 (96.7)	1,850 (96.6)
2 or more	1,575 (82.5)	1,574 (82.2)
3 or more	1,001 (52.5)	987 (51.5)
4 or more	435 (22.8)	443 (23.1)
5	97 (5.1)	102 (5.3)

Number of participants missing data (pioglitazone, placebo): HbA_{1c} (1, 0); abdominal obesity (22, 17); antihypertensive medication or blood pressure (6, 4); HDL (5, 3); triglycerides (4, 3); number of metabolic syndrome characteristics (31, 21). DBP, diastolic blood pressure; SBP, systolic blood pressure. *Waist circumference >102 cm for men and >88 cm for women.

99.7 ± 16.6 mg/dL (5.54 ± 0.92 mmol/L) with placebo ($P < 0.0001$).

Progression to diabetes occurred less often in participants in the pioglitazone versus placebo group: 73 (3.8%) vs. 149 (7.7%) (HR 0.48 [adjusted 95% CI 0.33–0.69]; adjusted *P* value <0.0001) (Table 2). As seen in Fig. 1*A*, divergence of the survival curves occurred as early as the first year, when the first mandatory FPG follow-up assessment was obtained. The same reduction in diabetes was observed in the ancillary analysis allowing for the 2010 updated ADA diagnostic criteria (HR 0.49 [unadjusted 95% CI 0.38–0.64]) (Supplementary Table 3).

Subgroup Analyses

Participants with IFG at baseline were more likely to develop diabetes during the trial in both randomized groups, when compared with patients with normal FPG. In those with IFG at baseline by the ADA criterion (≥100 mg/dL [5.6 mmol/L]) (18), diabetes was diagnosed in 6.5% in the pioglitazone group compared with 15.0% in the placebo group (HR 0.41 [95% CI 0.30–0.57]; $P < 0.0001$). In those with FPG <100 mg/dL at baseline, diabetes was diagnosed in 1.8 and 2.6%, respectively (HR 0.69 [0.39–1.23]; $P = 0.21$) (Table 2 and Fig. 1*B*). When IFG was defined as ≥110 mg/dL (6.1 mmol/L) to correspond to WHO/IDF criteria (19), 11.6 and 25.7% of the respective treatment groups were diagnosed with diabetes (HR 0.42 [0.27–0.64]; $P < 0.0001$). The corresponding values in those with FPG <110 mg/dL were 2.5 and 4.9% (HR 0.50 [0.34–0.72]; $P = 0.0002$). For both IFG subgroup analyses, there was no statistical heterogeneity of the response to pioglitazone in those with versus without prediabetes (interactions: ADA, $P = 0.11$; WHO/IDF, $P = 0.53$.) Similarly, there was no significant modification of the effect of pioglitazone on progression to diabetes according to other baseline metabolic subgroups examined, such as HbA_{1c} (Table 2 and Fig. 1*C*), HOMA-IR (Table 2 and Fig. 1*D*), and presence/absence of metabolic syndrome (Table 2). Nonetheless, because of the much higher rates of progression among all participants with IFG, higher HbA_{1c} or HOMA levels, and metabolic syndrome, the overall effect of pioglitazone was largely driven by its effect in these higher risk categories (Fig. 1).

There was no interaction between most other baseline features and the effect of pioglitazone to reduce diabetes risk (Fig. 2). The sole exception was that study participants randomized to pioglitazone who took at least 80% of the protocol dose of study drug (according to pill counts) were less likely to develop diabetes (1.6%) compared with equally adherent participants in the placebo group (7.6%) (HR 0.20 [95% CI 0.11–0.34]; $P < 0.0001$). Among less adherent participants, the HR for pioglitazone versus placebo was 0.70 (95% CI 0.49–1.00; $P = 0.04$) (interaction $P = 0.0002$).

In 1,460 participants with ADA-defined IFG at baseline and at least one postrandomization glucose test performed, persistent reversion to normal FPG occurred in 194 of 728 (26.6%) participants in the pioglitazone group and 88 of 732 (12.0%) participants in the placebo group ($P < 0.0001$). The corresponding rates using the WHO/IDF definition for IFG were 109 of 235 (46.4%) and 42 of 235 (17.9%), respectively ($P < 0.0001$). When we focused solely on those patients with no missing glucose data (i.e., with all yearly fasting glucose levels obtained), persistent reversion from IFG per ADA criteria to normal FPG occurred in 113 of 647 (17.5%) participants in the pioglitazone group and 42 of 686 (6.1%) participants in the placebo group ($P < 0.0001$). The corresponding rates using the WHO/IDF definition for IFG were 74 of 200 (37.0%) and 26 of 219 (11.9%), respectively ($P < 0.0001$).

Risk Factors for Diabetes

In bivariate analysis, several participant baseline features in IRIS were associated with increased risk for developing diabetes during the trial (Supplementary Table 4). In multivariable analysis, the following features were identified as independent predictors: younger age, larger waist circumference, higher FPG or HbA_{1c}, lower HDL cholesterol, and randomization to placebo.

Safety

As previously reported (7), patients randomized to pioglitazone experienced more weight gain, edema, and bone fractures compared with placebo. The maximum

Table 2—Progression to diabetes by treatment group (overall and by baseline glycemic/metabolic categories)

	Pioglitazone			Placebo						
		Diabetes			Diabetes					
	N	*N*	Percent	*N*	*N*	Percent	Risk Δ	*P* value*	HR (95% CI)†	*P* interaction‡
All participants	1,939	73	3.8	1,937	149	7.7	−3.9%	<0.0001	0.48 (0.33–0.69)	NA
ADA IFG										0.11
Present (≥100 mg/dL [5.6 mmol/L])	813	53	6.5	800	120	15.0	−8.5%	<0.0001	0.41 (0.30–0.57)	
Absent (<100 mg/dL [5.6 mmol/L])	1,126	20	1.8	1,137	29	2.6	−0.8%	0.21	0.69 (0.39–1.23)	
WHO/IDF IFG										0.53
Present (≥110 mg/dL [6.1 mmol/L])	267	31	11.6	257	66	25.7	−14.1%	<0.0001	0.42 (0.27–0.64)	
Absent (<110 mg/dL [6.1 mmol/L])	1,672	42	2.5	1,680	83	4.9	−2.4%	0.0002	0.50 (0.34–0.72)	
HbA_{1c}										0.57
≥5.7% (39 mmol/mol)	1,266	63	5.0	1,247	132	10.6	−5.6%	<0.0001	0.46 (0.34– 0.62)	
<5.7% (39 mmol/mol)	672	10	1.5	690	17	2.5	−1.0%	0.17	0.58 (0.27, 1.28)	
HOMA										0.10
≥4.6§	1,006	47	4.7	989	109	11.0	−6.3%	<0.0001	0.40 (0.29–0.57)	
<4.6	933	26	2.8	948	40	4.2	−1.4%	0.10	0.66 (0.40–1.08)	
Metabolic syndrome‖										0.99
Present	1,001	56	5.6	987	113	11.4	−5.8%	<0.0001	0.46 (0.33–0.63)	
Absent	907	15	1.7	929	34	3.7	−2.0%	0.01	0.46 (0.25–0.84)	

NA, not applicable. **P* value for log-rank test. †CI for overall effect is adjusted for multiplicity; other CIs are not adjusted. ‡*P* value is the test for interaction between treatment and each subgroup. §Median value for HOMA in IRIS participants. ‖At least three NCEP ATP-III metabolic syndrome features present.

difference in weight change was seen at year 4: those in the pioglitazone group gained an average of 5.8 lb (2.6 kg), and those in the placebo group lost an average of 1.2 lb (0.5 kg) ($P < 0.001$). Edema (35.6 vs. 24.9% [$P < 0.001$]) and bone fractures requiring hospitalization or surgery (5.1 vs. 3.2% [$P = 0.003$]) also occurred more frequently in the pioglitazone group. Despite the greater incidence of edema, there was no increase in heart failure (74 vs. 71 patients, respectively [$P = 0.80$]) or in hospitalization for heart failure (50 vs. 41 patients, respectively [$P = 0.34$]). Incident bladder cancer was diagnosed in 12 (0.6%) participants in the pioglitazone group and 8 (0.4%) in the placebo group. ($P = 0.37$). Overall cancer incidence was also not different in the two groups (133 [6.9%] vs. 150 [7.7%] patients, respectively [$P = 0.29$]).

Adherence to Study Drug

Patients randomized to pioglitazone were less likely to stay on study drug compared with those randomized to placebo (5). At 1 year, the proportions of participants still taking the study drug were 76 and 85%, respectively, decreasing to 60 and 67%, respectively, at the final visit. More participants in the pioglitazone group stopped study drug because of edema or weight gain (172 vs. 51 on placebo), and more were removed from active therapy for safety concerns (146 vs. 117 participants). The median dose by year taken in the pioglitazone group during the trial ranged between 29 and 40 mg/day.

CONCLUSIONS

In this clinical trial of patients without diabetes who had insulin resistance along with ischemic stroke or TIA, therapy with pioglitazone reduced the risk of diabetes by 52% during a median follow-up of 4.8 years. This appeared to be predominately driven by a larger effect in participants with greater risk of progression to diabetes, such as individuals with prediabetes or worse insulin resistance at baseline. The absence of a statistically significant interaction between baseline FPG or baseline HbA_{1c} and treatment effect does suggest that pioglitazone may prevent not only the conversion of prediabetes to diabetes but also the development of diabetes in normoglycemic individuals who have insulin resistance. The absolute risk reduction in the latter category is, however, small.

In previous trials, troglitazone (Diabetes Prevention Program [DPP]) (20), rosiglitazone (Diabetes REduction Assessment with ramipril and rosiglitazone Medication [DREAM]) (21), and pioglitazone (Actos Now for Prevention of Diabetes [ACT NOW]) (22) reduced the progression to diabetes in patients with impaired glucose tolerance or IFG by 60–75% over a period of 0.9–3 years (6,20). Another trial (TRoglitazone in the Prevention of Diabetes [TRIPOD]) (23) in women with previous gestational diabetes and an abnormal OGTT showed that troglitazone reduced progression to diabetes by 55% over 2.5 years. These previous diabetes prevention studies enrolled participants with prediabetes but without overt cardiovascular disease. The IRIS trial documents the preventive effect of thiazolidinediones in patients with cerebrovascular disease and insulin resistance.

The IRIS study design did not include any glycemic assessments after conclusion of the randomized treatment period, so we do not know if pioglitazone had a sustained preventive effect or a temporary suppressive effect on the progression of hyperglycemia. The former was demonstrated with troglitazone in the TRoglitazone in the Prevention of Diabetes trial and was attributed to preservation of the β-cell function. In contrast, however, in the Diabetes Prevention Program, Diabetes REduction Assessment with ramipril and rosiglitazone Medication, and Actos Now for Prevention of Diabetes trials, the effect of therapy did not appear to persist after drug discontinuation (20,24,25).

We initially hypothesized that, through its insulin-sensitizing effects, pioglitazone therapy would result in both a reduction

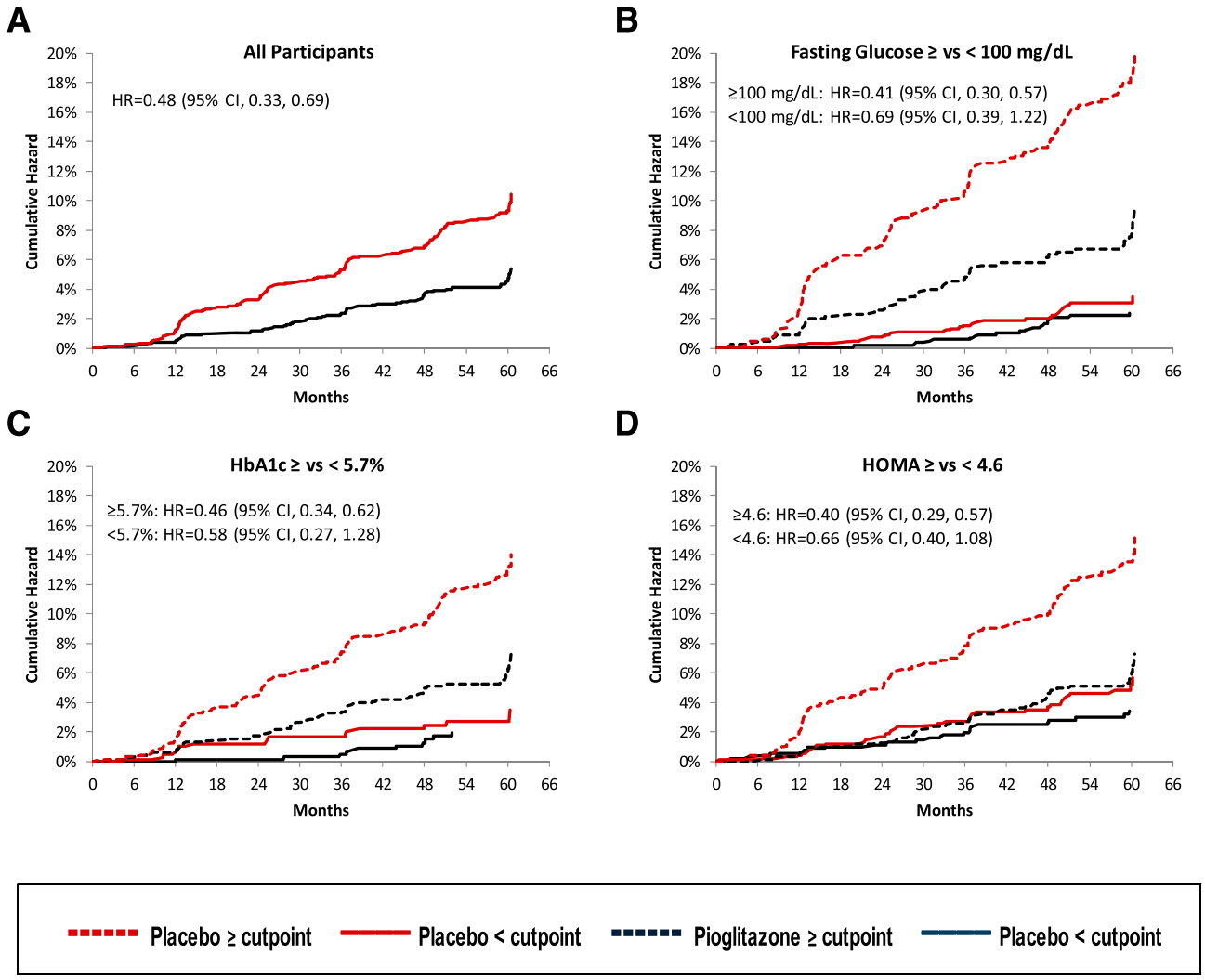

Figure 1—Time to diabetes onset: overall and by metabolic subgroups. *A* shows the overall onset of diabetes by treatment group. *B–D* show similar data, with treatment groups further subdivided by baseline metabolic category. *B*: With or without IFG using ADA criteria. *C*: HbA_{1c} above or below the ADA prediabetes cut point of 5.7%. *D*: Those above versus below the median HOMA-IR value of 4.6, with the former denoting greater insulin resistance. (Blue lines depict the pioglitazone group and red lines the placebo group. Except for *A*, solid lines indicate the subgroup below the cut point for the variable, whereas dashed lines indicate the subgroup above the cut point.)

in cardiovascular events and the incidence of diabetes (26,27). Our results are consistent with this hypothesis. The mechanism(s), however, by which pioglitazone improved cardiovascular outcomes in IRIS (7) remains uncertain. Our findings to date cannot easily elucidate the extent to which insulin sensitization may have mediated the observed cardiovascular benefits. However, it seems unlikely that glucose lowering in this range or diabetes prevention per se can be directly credited, based on prior studies involving the therapy of early diabetes in patients at high cardiovascular risk (28). Given the relatively small number of events for both cardiovascular outcomes and the development of diabetes, further statistical inquiry into their potential relationship will be difficult to interpret. In fact, pioglitazone demonstrated several other benefits beyond glucose control. It lowered blood pressure and C-reactive protein and increased HDL cholesterol, each of which might have promoted cardiovascular health (7). Previous studies involving direct measures of atheroma volume in patients with and without diabetes have suggested a possible direct vascular effect of pioglitazone (29,30). It is therefore also possible that pioglitazone attenuates the progression of atherosclerosis through peroxisome proliferator–activated receptor-γ activation in the vasculature (31) and/or in inflammatory cells (32), concurrent with (but not necessarily stemming from) its metabolic actions mediated through peroxisome proliferator–activated receptor-γ in adipocytes, skeletal muscle, and the liver.

IRIS was designed primarily as a secondary stroke prevention trial and has obvious limitations as regards to metabolic assessment of participants. First, some patients likely already had mild diabetes at study initiation because we did not perform OGTTs. We also did not use this test to monitor for diabetes during follow-up. Had we performed OGTTs at baseline and annually, it is likely that more patients would have been excluded for diabetes at screening, and more participants would have converted to diabetes during follow-up. However, it seems unlikely that our

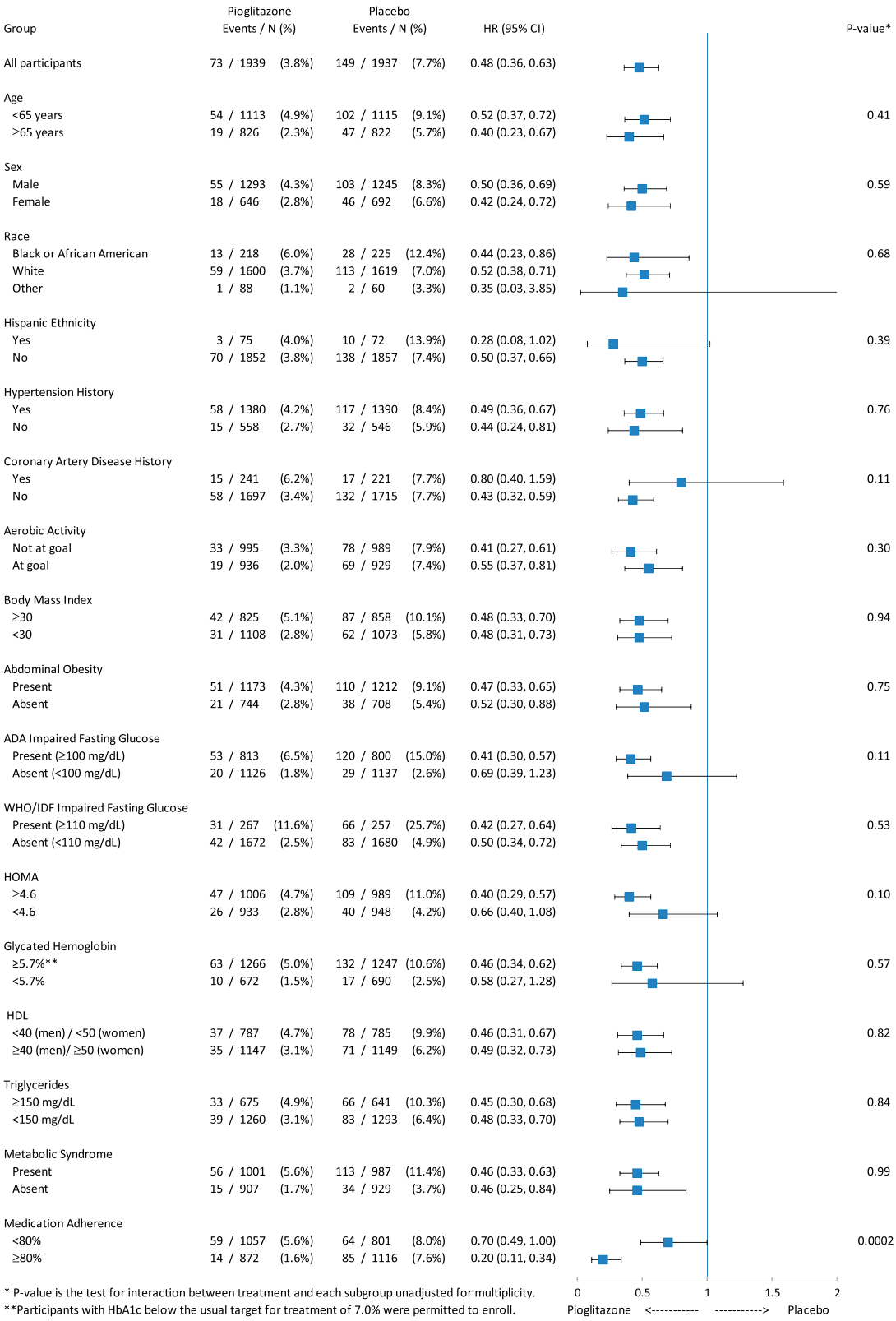

Figure 2—Subgroup analysis. Treatment effect for progression to diabetes is displayed between the two randomized categories (pioglitazone vs. placebo) by important subgroups. No heterogeneity of effect is demonstrated, with the exception of a significant interaction with degree of study drug adherence.

findings would have changed substantially based on the similar risk reductions observed in previous thiazolidinedione studies that did use the OGTT (21,22). At a practical level, few clinicians routinely use OGTT in surveillance for development of diabetes, so the IRIS results may better reflect the outcomes that would be seen in the real-world setting. Second, we also did

not use $HbA_{1c} \geq 6.5\%$ as an exclusion, nor did we measure HbA_{1c} beyond the screening visit, because this test was not sanctioned for diabetes diagnosis by the ADA until 2010 (9). It is also likely that conversion to diabetes would have been detected in more of our participants if we had measured HbA_{1c} during follow-up. In an ancillary analysis, however, using the updated diagnostic criteria outside of trial testing, the effect of pioglitazone on diabetes onset was unchanged. Third, our definition of diabetes permitted the diagnosis by the patient's personal physician or during hospitalizations based on prespecified criteria. This required a nonstandardized adaption of prevailing diagnostic criteria through which we attempted to balance accuracy with the pragmatic considerations of a large, multicenter trial.

Adherence to study drug was also not ideal in IRIS, a reflection of the known side effect profile of pioglitazone (33), increasing media attention about possible risks (11), and our cautious approach in discontinuing study drug in participants experiencing or felt to be at high risk for adverse events. In our cohort of older patients with cerebrovascular disease, we observed more weight gain, edema, and bone fracture in pioglitazone compared with placebo-treated patients. However, we did not observe an increase in heart failure events, a concern with all thiazolidinediones (34,35), likely due to our conservatism in the selection and management of participants as well as the low prevalence (~12%) of known coronary artery disease in in the IRIS cohort (7). Incident bladder cancer, a topic with conflicting evidence concerning this medication (36,37), as well as any cancer occurred with similar frequency between the two groups, although IRIS was not powered to assess the effect of pioglitazone on specific neoplasms. Overall, our adherence rates were not dissimilar to those reported in large observational studies of a variety of glucose-lowering drugs in patients with type 2 diabetes (38) as well as from diabetes prevention trials with this class of medication (21,22). As suggested by our analysis of adherent versus nonadherent participants, if adherence to the study drug had been higher, we might have observed a larger risk reduction for diabetes but also, of course, potentially more adverse effects.

In summary, pioglitazone approximately halved the risk of developing diabetes in patients with insulin resistance and cerebrovascular disease. The absolute diabetes risk was highest in those with IFG, increased HbA_{1c}, higher HOMA-IR (indicating more insulin resistance), and metabolic syndrome, so the preventive effect of pioglitazone was predominately driven by patients in these higher risk categories. Pioglitazone is the first pharmacological agent demonstrated in a single trial to both prevent diabetes and improve cardiovascular outcomes in patients at increased risk for these sequelae. More broadly, our results lend support to the notion that diabetes prevention through insulin sensitization could potentially be associated with important cardiovascular benefits.

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